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<p>(21) International Application Number: PCT/US00/05881</p> <p>(22) International Filing Date: 8 March 2000 (08.03.00)</p> <p>(30) Priority Data: 60/124,270 12 March 1999 (12.03.99) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Laytonsville, MD 20882 (US).</p> <p>(74) Agents: WALES, Michele, M. et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: HUMAN BREAST AND OVARIAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES</p> <p>(57) Abstract</p> <p>This invention relates to newly identified breast, ovarian, breast cancer and/or ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, particularly disorders of the breast and/or ovary, including the presence of breast cancer and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, particularly disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.</p>			

designated BRCA1 and BRCA2, have been isolated and characterized. BRCA1 is at 17q21 (Claus et al, Am. J. Epidemiology 131:961 (1990); Hall et al, Science 250:1684 (1990); Easton et al, Am. J. of Human Genetics 52 (4):678 (1993); Black et al, Am. J. of Human Genetics 52 (4):702 (1993); Bowcock et al, Am. J. of Human Genetics 52 (4):718 (1993); 5 Miki et al, Science 266:66 (1995)). The demonstration of loss of heterozygosity (LOH) at 17q25 has defined another potential tumor suppressor gene (Lindblom et al, Human Genetics 91:6 (1993); Cornelis et al, Oncogene 8:781 (1993); Theile et al, Oncogene 10:439 (1995)).

There is a need, therefore, for identification and characterization of such factors that modulate activation and differentiation of breast and ovarian cells, both normally and in 10 disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

The present invention relates at least in part, to a novel breast and ovarian and breast 15 and ovarian cancer related polynucleotides and polypeptides. The discovery of these breast and ovarian cancer related polynucleotides provides new compositions which are useful in the diagnosis, prevention and treatment of disorders of the female reproductive system, particularly of the ovary including, but not limited to ovarian cancer, and the breast, including but not limited to breast cancer.

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Summary of the Invention

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a breast, ovarian, breast cancer and/or ovarian cancer associated 25 polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 418) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a 30 polynucleotide encoding a breast, ovarian, breast cancer, and/or ovarian cancer polypeptide. The present invention further includes breast, ovarian, breast cancer, and/or ovarian cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid

sequences comprising, or alternatively consisting of, breast, ovarian, breast cancer, and/or ovarian cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 419 to 836) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention.

5 Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the female reproductive system, specifically disorders related to the breast and/or ovary, including breast cancer

10 and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention.

Detailed Description

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Tables

Table 1 summarizes some of the breast/ovarian cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the breast/ovarian cancer 20 polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification 25 of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as 30 SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence

<211> 465
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 676

Asn Asp Ser Leu Xaa Xaa Lys Ala Gly Thr Pro Ala Gly Asn Arg Xaa
1 5 10 15

Gly Ile Pro Gly Ser Thr His Ala Ser Ala Ala Ala Pro Phe Ala Ala
20 25 30

Ala Leu Ala Arg Asp Pro Asn Pro Ala Ser Pro Leu Pro Glu His Arg
35 40 45

Pro Arg Leu His Arg Gly Pro Gly Pro Pro Ala Arg Leu Ala Ala Ala
50 55 60

Met Ala Asp Pro Lys Tyr Ala Asp Leu Pro Gly Ile Ala Arg Asn Glu
65 70 75 80

Pro Asp Val Tyr Glu Thr Ser Asp Leu Pro Glu Asp Asp Gln Ala Glu
85 90 95

Phe Asp Ala Glu Glu Leu Thr Ser Thr Ser Val Glu His Ile Ile Val
100 105 110

Asn Pro Asn Ala Ala Tyr Asp Lys Phe Lys Asp Lys Arg Val Gly Thr
115 120 125

Lys Gly Leu Asp Phe Ser Asp Arg Ile Gly Lys Thr Lys Arg Thr Gly
130 135 140

Tyr Glu Ser Gly Glu Tyr Glu Met Leu Gly Glu Gly Leu Gly Val Lys
145 150 155 160

Glu Thr Pro Gln Gln Lys Tyr Gln Arg Leu Leu His Glu Val Gln Glu

	165	170	175
Leu Thr Thr Glu Val Glu Lys Ile Lys Thr Thr Val Lys Glu Ser Ala			
180	185	190	
Thr Glu Glu Lys Leu Thr Pro Val Leu Leu Ala Lys Gln Leu Ala Ala			
195	200	205	
Leu Lys Gln Gln Leu Val Ala Ser His Leu Glu Lys Leu Leu Gly Pro			
210	215	220	
Asp Ala Ala Ile Asn Leu Thr Asp Pro Asp Gly Ala Leu Ala Lys Arg			
225	230	235	240
Leu Leu Leu Gln Leu Glu Ala Thr Lys Asn Ser Lys Gly Gly Ser Gly			
245	250	255	
Gly Lys Thr Thr Gly Thr Pro Pro Asp Ser Ser Leu Val Thr Tyr Glu			
260	265	270	
Leu His Ser Arg Pro Glu Gln Asp Lys Phe Ser Gln Ala Ala Lys Val			
275	280	285	
Ala Glu Leu Glu Lys Arg Leu Thr Glu Leu Glu Thr Ala Val Arg Cys			
290	295	300	
Asp Gln Asp Ala Gln Asn Pro Leu Ser Ala Gly Leu Gln Gly Ala Cys			
305	310	315	320
Leu Met Glu Thr Val Glu Leu Leu Gln Ala Lys Val Ser Ala Leu Asp			
325	330	335	
Leu Ala Val Leu Asp Gln Val Glu Ala Arg Leu Gln Ser Val Leu Gly			
340	345	350	
Lys Val Asn Glu Ile Ala Lys His Lys Ala Ser Val Glu Asp Ala Asp			
355	360	365	
Thr Gln Ser Lys Val His Gln Leu Tyr Glu Thr Ile Gln Arg Trp Ser			
370	375	380	
Pro Ile Ala Ser Thr Leu Pro Glu Leu Val Gln Arg Leu Val Thr Ile			
385	390	395	400
Lys Gln Leu His Glu Gln Ala Met Gln Phe Gly Gln Leu Leu Thr His			
405	410	415	
Leu Asp Thr Thr Gln Gln Met Ile Ala Asn Ser Leu Lys Asp Asn Thr			
420	425	430	
Thr Leu Leu Thr Gln Val Gln Thr Met Arg Glu Asn Leu Ala Thr			

648

435

440

445

Val Glu Gly Asn Phe Ala Ser Ile Asp Glu Arg Met Lys Lys Leu Gly
450 455 460

Lys
465

<210> 677
<211> 48
<212> PRT
<213> Homo sapiens

<400> 677
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1 5 10 15

Ala Phe Ser Phe Thr Thr Lys Glu Arg Asp Gln Lys Pro Leu Ile Phe
20 25 30

Asn Phe His Lys Met Leu Glu Val Tyr Ile Tyr Ile Tyr Ile Phe Leu
35 40 45

<210> 678
<211> 940
<212> PRT
<213> Homo sapiens

<400> 678
Val Leu Gly Glu Gly Ile Ser Phe Leu Leu Ser Pro Pro Leu Pro Thr
1 5 10 15

Pro Ser Ile Asn Ile Ile Leu Leu Lys Ile Leu Arg Cys Gln Ala Ala
20 25 30

Lys Val Glu Ser Ala Ile Ala Glu Gly Gly Ala Ser Arg Phe Ser Ala
35 40 45

Ser Ser Gly Gly Gly Ser Arg Gly Ala Pro Gln His Tyr Pro Lys
50 55 60

Thr Ala Gly Asn Ser Glu Phe Leu Gly Lys Thr Pro Gly Gln Asn Ala
65 70 75 80